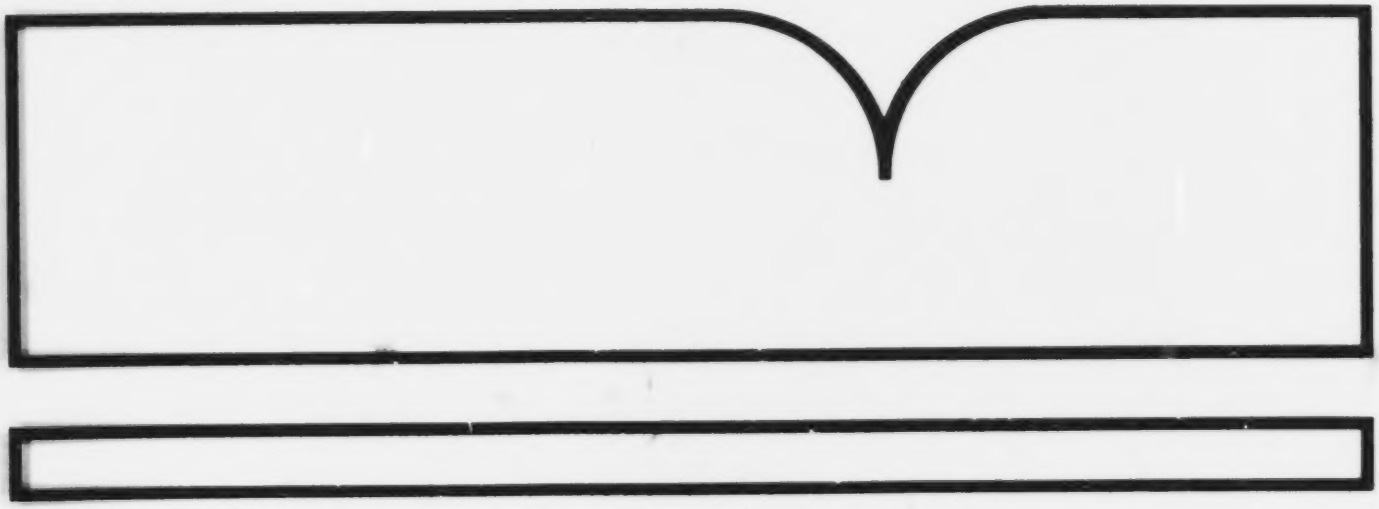
PB83-193839

Trimethyltin, a Selective Limbic System Neurotoxicant, Impairs Radial-Arm Maze Performance

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

1982



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA-600/J-82-309	2. JOURNAL ARTICLE	3. RE PB83-133839
4. TITLE AND SUBTITLE Trimethyltin, a Selective Limbic System Neurotoxicant, Impairs Radial-Arm Maze Performance		5. REPORT DATE 1982 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Thomas Walsh, Diane Miller, and Robert Dyer		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Neurotoxicology Division Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711		10. PROGRAM ELEMENT NO. ACSL1A 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Research and Development Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, NC 27711		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE EPA-600/11

15. SUPPLEMENTARY NOTES

Published In: Neurobehavioral Toxicology and Teratology, Vol. 4, 177-183, 1982

16. ABSTRACT

Rats were trained for fifteen sessions in an automated eight arm radial maze prior to treatment with 6 mg/kg trimethyltin chloride. This compound is a neurotoxicant which primarily damages the limbic system, in particular pyramidal cells in the CA3 region of the hippocampus. Following treatment the animals exhibited a marked and persistent impairment of maze performance characterized by decreased selection accuracy and an altered spatial pattern of responding within the maze. These results offered additional evidence that CA3 pyramidal neurons or their connections play an imporant, if not essential, role in radial-arm maze performance. It was suggested that trimethyltin might be a useful tool for elucidating the neural substrates of both radial maze performance and learning and memory processes.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Release to Public	Unclassified	8
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA-600/J-82-309
JOURNAL ARTICLE

Neurobehavioral Toxicology and Teratology, Vol. 4, pp. 177–183, 1982. Printed in the U.S.A.

Trimethyltin, a Selective Limbic System Neurotoxicant, Impairs Radial-Arm Maze Performance[1]

THOMAS J. WALSH,[2] DIANE B. MILLER AND ROBERT S. DYER

Neurotoxicology Division (MD-74B), Health Effects Research Laboratory
U. S. Environmental Protection Agency, Research Triangle Park, NC 27711

WALSH, T. J., D. B. MILLER AND R. S. DYER. *Trimethyltin, a selective limbic system neurotoxicant, impairs radial-arm maze performance.* NEUROBEHAV. TOXICOL. TERATOL. 4(2) 177–183, 1982.—Rats were trained for fifteen sessions in an automated eight arm radial maze prior to treatment with 6 mg/kg trimethyltin chloride. This compound is a neurotoxicant which primarily damages the limbic system, in particular pyramidal cells in the CA3 region of the hippocampus. Following treatment the animals exhibited a marked and persistent impairment of maze performance characterized by decreased selection accuracy and an altered spatial pattern of responding within the maze. These results offered additional evidence that CA3 pyramidal neurons or their connections play an important, if not essential, role in radial-arm maze performance. It was suggested that trimethyltin might be a useful tool for elucidating the neural substrates of both radial maze performance and learning and memory processes.

Trimethyltin Radial-arm maze Organotins Memory Spatial memory Neurotoxicology
Limbic system Hippocampus

TRIMETHYLTIN (TMT) is a neurotoxic organometal which produces a variety of neurobehavioral effects in both laboratory animals and man. This compound, although not commercially used in either the United States or Europe, is a common intermediate and byproduct in the synthesis of other organotins and several episodes of human exposure have been reported [6, 10, 30]. Accidental exposure to TMT in the workplace has been reported to produce a neurologic syndrome consisting of spontaneous seizures, emotional lability, anorexia and learning and memory impairments [11,31]. We recently reported that a similar constellation of behavioral changes is evident in the rat following acute exposure to TMT [8]. These neurotoxic effects have been attributed to the limbic system toxicity of this compound. For example, several investigators [4,5] have observed a unique pattern of limbic system damage involving the hippocampus, amygdala and pyriform cortex following either acute or chronic TMT exposure in rats. Furthermore, within the hippocampus there is a gradient of sensitivity such that pyramidal cells in area CA3 are particularly vulnerable to the neurotoxic properties of TMT [7]. The presumed involvement of the hippocampus in behavioral and neural plasticity [34,35] suggested the possibility that TMT's toxic interaction with this limbic forebrain structure might be responsible for its reported effects on learning and memory.

In the present series of experiments we examined the effects of TMT on the retention and performance of a radial-arm maze task. This paradigm has proved to be a sensitive indicator of hippocampal dysfunction and is believed to be particularly useful in assessing deficits in short-term or "working" memory (for review see [26]).

METHOD

Subjects

Eighteen male Long-Evans hooded rats obtained from Charles River Breeders (Wilmington, MA) were used in the present study. All rats were individually housed in plastic cages with wood chip bedding in a temperature and humidity controlled animal colony under a 12-hr/12-hr light/dark cycle. Laboratory chow and water were freely available until the start of behavioral testing.

Apparatus

The apparatus used was an automated eight arm radial maze modified from one described by Olton and Samuelson [28]. The maze consisted of an octagonal central arena (32 cm dia./7.5 cm side) from which radiated eight equally spaced alleys (26 cm long × 10.5 cm wide × 9.5 cm high) (Fig. 1). At the end of each alley was a trough connected to a Gerbrands pellet dispenser which delivered 45 mg food pellets (Noyes Co., Lancaster, NH). The base of the apparatus was constructed of black Plexiglas and the top covering of

[1]This manuscript has been reviewed by the Health Effects Research Laboratory, U. S. Environmental Protection Agency and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

[2]To whom requests for reprints should be addressed.

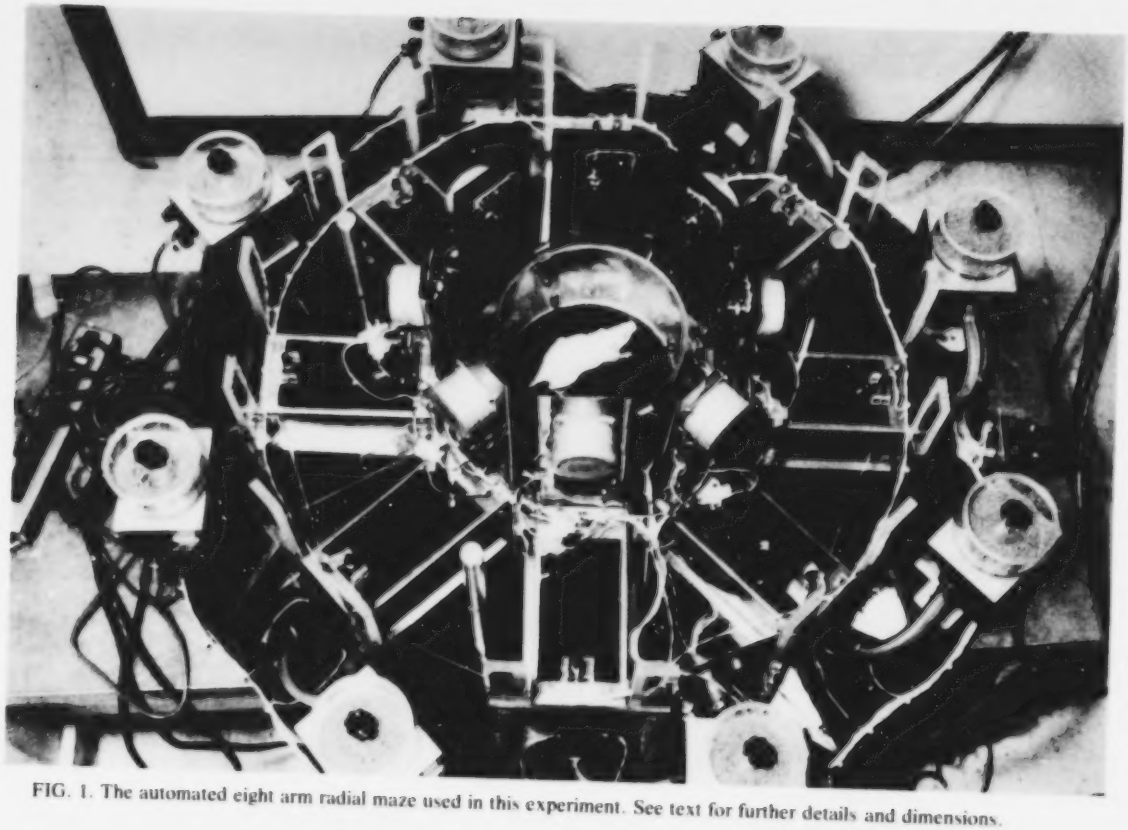


FIG. 1. The automated eight arm radial maze used in this experiment. See text for further details and dimensions.

clear Plexiglas. Entry into the arms was controlled by motor driven guillotine doors. The time of each feeder entry and the rate of locomotor activity within the maze were detected by LED/photodiode circuits in the following locations: 8 in the central arena, 1 at the entry to each alley and 1 in each pellet trough.

Operation of the doors and pellet dispensers and the collection of experimental data was controlled by a programmed North Star Horizon microprocessor.

Procedure

Baseline acquisition. Prior to acquisition animals were gradually reduced to 85% of their free-feeding body weight by limiting their daily ration of food. During each test session a rat was placed into the central arena of the maze with the doors closed and access to the arms and feeders blocked. Within ten seconds thereafter the program was initiated, the entry arms automatically opened and a food pellet was delivered to each of the feeders. A trial was ended following entry into all eight feeders or after ten minutes, whichever came first. The following dependent measures were automatically recorded: (1) number of correct (i.e., non-repeated) feeder selections within the first eight choices, (2) total number of feeder selections necessary to obtain all eight pellets, (3) a measure of temporal efficiency or rate of correct selections, and (4) averaged locomotor activity (responses/minute) within the session. Immediately following each test session the rats were given a ration of food to maintain their body weight. The rats were trained for fifteen days in the maze. Testing was performed approximately the same time every day (Monday–Friday). Following these acquisition sessions the animals were divided into two groups (n=8 per group), which were equated for selection accuracy and level of locomotor activity in the maze during the test sessions. On the following Monday animals were intragastrically intubated with either 0 (physiological saline) or 6 mg/kg TMT Cl (dosage calculated as the base). TMT chloride was obtained from K&K Laboratories (Plainview, NY) and administered in a volume of 1 ml/kg body weight. Two weeks followed dosing before the resumption of behavioral testing so that the rats could recover from the acute phase of TMT-induced toxicity [8]. During this time all rats had ad lib access to food and water.

Reacquisition 1. Prior to the beginning of the first reacquisition phase (days 15–35 post-dosing) animals were again reduced to 85% of their newly acquired free-feeding weight. During Reacquisition 1 the rats were again trained for a total of fifteen sessions in the maze using the same daily protocol as during acquisition.

Reacquisition 2. To determine whether deficits in maze performance following TMT were transient and reversible with either extended training or time the rats were retrained in the maze for another fifteen sessions fourteen days following the completion of Reacquisition 1 (days 49–70 post-dosing).

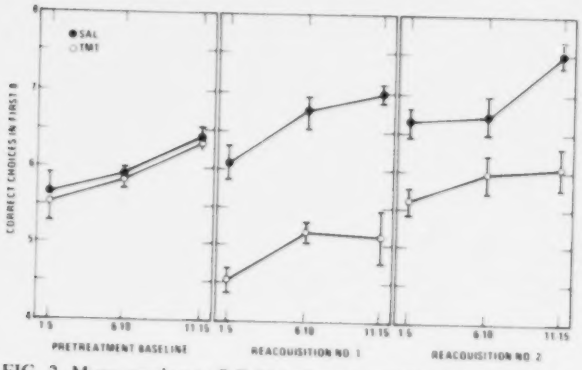


FIG. 2. Mean number (±S.E.M.) of non-repeated feeder entries in the first eight choices for the three phases of this experiment. The data for this figure and Figs. 3, 4 and 5 were summarized for each block of five sessions (i.e., 1–5, 6–10, 11–15).

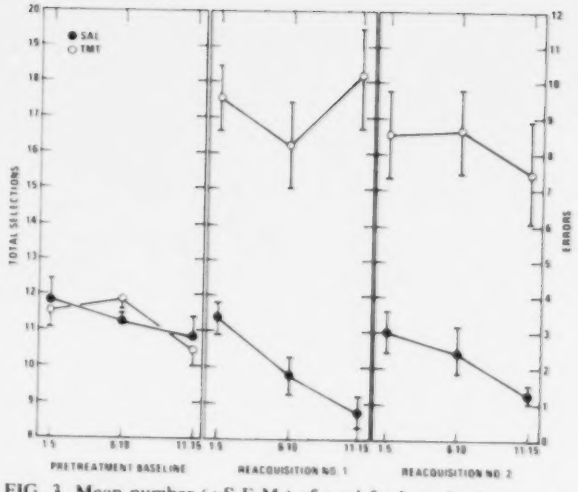


FIG. 3. Mean number (±S.E.M.) of total feeder selections necessary to obtain all eight pellets within a session.

Data Analysis

Data from the three phases of behavioral testing (Baseline Acquisition, Reacquisition 1 and Reacquisition 2) were treated as independent data sets. Each data set was analyzed for overall treatment, time (weeks) and treatment × week interaction effects by multivariate analysis of variance (MANOVA) procedures using Wilk's Criterion. Significant Bonferroni-corrected MANOVAs ($\alpha = 0.05/3 = 0.016$) were followed by repeated measures ANOVAs using weeks as the repeated factor. Signficant ANOVAs were followed by appropriate group by group comparisons using Duncan's Multiple Range test. The experiment-wise error rate was maintained at 0.05.

Histology

Thirty-five days following the completion of behavioral testing (i.e., 105 days after dosing) all rats were perfused through the heart with saline followed by neutral buffered Formalin. Frozen sagittal sections (40 μ), obtained from one hemisphere, were stained with cresyl violet for histological evaluation. In this report the only measure of hippocampal morphology to be presented will be the length of the pyramidal cell line measured from the CA1-Subiculum border to the point where the organized line of pyramidal cells was no longer readily discriminable (i.e., CA3c in normal tissue). This measure was chosen since it has been shown to be the most dose-related indicator of hippocampal pathology following TMT [7]. A more complete description of the hippocampal damage in the TMT-treated rats used in this experiment can be found in Dyer *et al.* [7].

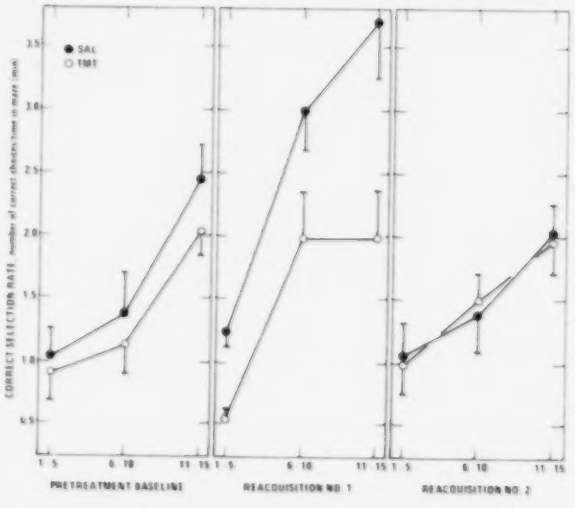


FIG. 4. Mean (±S.E.M.) index of temporal efficiency of maze performance. The index was calculated as the rate of correct selections per minute (number of correct choices/time in maze (min)).

RESULTS

Baseline Acquisition

During the pretreatment baseline period there were no significant between group differences, $F(4,11) = 0.26$, $p > 0.10$, or group × week interactions, $F(8,50) = 0.78$, $p > 0.10$; however, there was a significant week effect, $F(8,50) = 9.40$, $p < 0.0001$, indicating that maze performance did in fact change over time. Univariate ANOVAs revealed a signficant increase in the number of correct arms in the first eight choices, temporal efficiency and locomotor activity (all F's$(2,28) > 15.62$, all p's< 0.0001) but not number of total selections, $F(2,28) = 1.11$, $p > 0.10$, over weeks. These data demonstrate that prior to treatment both groups of rats were comparable on all measures of maze performance and locomotor activity within the maze. Furthermore, the significant main effect of weeks indicates, as can be seen in Figs. 2, 3, 4 and 5, that there was a progressive increase in selection accuracy and temporal efficiency coincident with an increased level of intramaze motor activity. By the end of the third week of testing both groups made approximately seven correct responses within the first eight arm choices and obtained

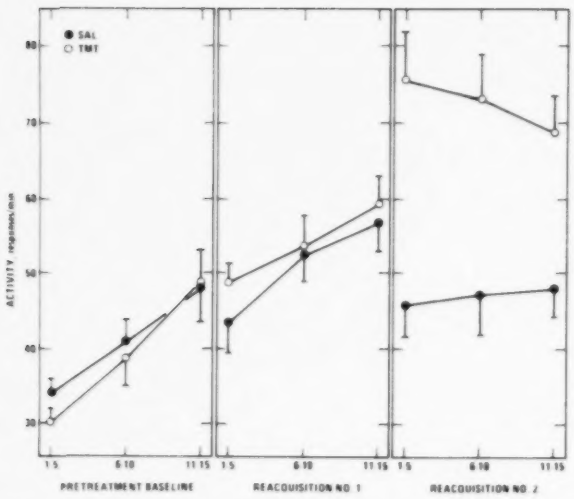


FIG. 5. Mean number (±S.E.M.) of photocell interruptions per minute in the maze.

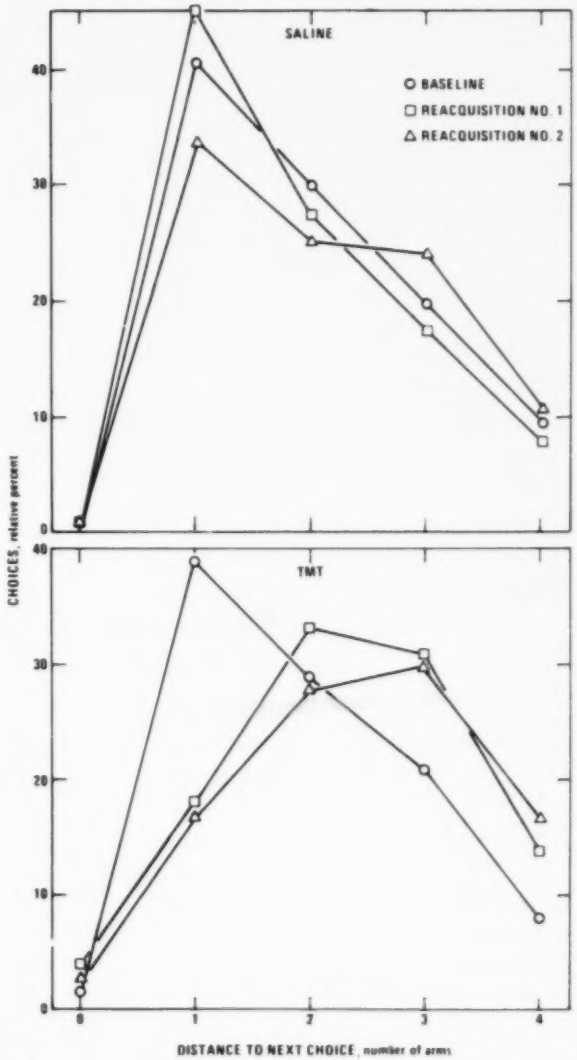


FIG. 6. The relative frequency of selecting feeders various distances (clockwise or counter-clockwise) from the one just exited (Arm 0).

all pellets within ten to eleven entries. It was also evident that response patterns were similar between groups. Both groups of animals exhibited a marked tendency to enter an arm immediately adjacent to the one just exited (Fig. 6). The lack of a signficant group × week interaction suggests that the rate of improvement in maze performance and the increase in activity were similar or parallel in both groups before dosing. The two groups acquired efficient maze performance at a similar rate and with the use of comparable response strategies.

Reacquisition 1

Following dosing the TMT-treated rats exhibited a transient period of weight loss and hyperexcitability. At the resumption of behavioral testing however, the treated animals were comparable in all overt respects to the controls.

In contrast to the baseline period, the maze performance of the two groups differed markedly during Reacquisition 1. The MANOVAs demonstrated signficant effects of both treatment, $F(4,11)=13.32$, $p<0.0003$, and weeks, $F(8,50)=5.31$, $p<0.0001$, but no treatment × week interaction, $F(8,50)=1.45$, $p>0.10$. Therefore, although the groups were different on certain measures of performance and/or locomotor activity, their rate of improvement was similar over time. ANOVAs revealed a significant treatment effect on total selections, number of correct arms in first eight choices and temporal efficiency (all $F's(1,14)>7.10$, all $p's<0.01$). An important finding of the present experiment was that no significant between group differences were evident on the activity measure, $F(1,14)=0.44$, $p>0.10$. Therefore, impaired maze performance was not secondary to TMT-induced activity changes.

The spatial pattern of responses was different for the two groups. The rats treated with TMT did not prefer the immediately adjacent arm but shifted their modal preference to the second arm away from the one just exited (Fig. 6).

ANOVAs demonstrated a significant effect of weeks on number of correct arms in the first eight choices, temporal efficiency and locomotor activity (all $F's(2,28)>9.54$, all $p's<0.0007$). These data again demonstrate that there were improvements in maze performance over time which were coincident with increased levels of activity. The rates of improvement were similar across the two groups, as indicated by the lack of a significant treatment × week interaction. The TMT-treated animals, however, required more selections to obtain the pellets, were less accurate in their selection of baited food arms and exhibited a less efficient temporal pattern of performance in the maze. These data demonstrate that while TMT markedly impairs maze performance it did not prevent improvement with further training.

TABLE 1

CORRELATION BETWEEN LENGTH OF PYRAMIDAL CELL LINE AND INDICES OF MAZE PERFORMANCE

Performance Measure	R	p	R^2	Condition
Total Selections	−.48	0.0009	.23	Reacquisition 1
	−.32	0.0306	.10	Reacquisition 2
Correct in First Eight	.46	0.0015	.21	Reacquisition 1
	.46	0.0013	.21	Reacquisition 2
Temporal Efficiency	−.36	0.0150	.13	Reacquisition 1
	−.16	0.29	.025	Reacquisition 2
Activity	.05	0.73	.0025	Reacquisition 1
	−.33	0.028	.108	Reacquisition 2

Reacquisition 2

During Reacquisition 2, the rats treated with TMT remained impaired, as during Reacquisition 1, but developed in addition a pronounced hyperactivity.

An overall MANOVA demonstrated a significant effect of treatment, $F(4,10)=6.22$, $p<0.0088$; however, neither the effects of week, $F(8,46)=1.98$, $p>0.05$, nor the treatment × week interaction, $F(8,46)=1.67$, $p>0.10$, were statistically significant. The absence of a week effect indicates that animals were already performing at an asymptotic level. Results of the ANOVAs indicated a significant treatment effect on total selections, number of correct responses in the first eight choices and locomotor activity (all F's$(1,13)>13.55$, all p's<0.0028).

Histology

Histological evaluation indicated extensive loss of hippocampal pyramidal cells, especially those of CA3, some loss of granule cells and shrinkage of the intrahilar space of the fascia dentata. Table 1 shows the Pearson Product Moment Correlations between one measure of hippocampal damage (i.e., length of the pyramidal cell line) and performance measures in the maze. The results indicate that although there were significant correlations between this measure of damage and performance in the maze, the percentage of variance accounted for by the length of the pyramidal cell line was relatively small. For example, although the correlation between hippocampal damage and number of correct arm selections in the first eight choices was highly significant (i.e., $R=.46$, $p<0.0015$), differences in the pyramidal cell line accounts for only about 21% of the variability in this behavioral measure.

DISCUSSION

The purpose of the present experiment was to examine the effects of trimethyltin, a neurotoxic organometal, on the performance of rats previously trained in a radial-arm maze task. The results of this experiment demonstrated that rats treated with TMT exhibited a marked and persistent impairment of radial-arm maze performance which was evident throughout the period of testing (i.e., up to 70 days post-treatment). This impairment was characterized by more repeated feeder entries in the first eight choices and a greater total number of selections needed to obtain all pellets within a given session. During the first reacquisition period the deficits in maze performance were not secondary to changes in locomotor activity, the ability to execute the appropriate responses or alterations in motivation. The rats treated with TMT performed the necessary responses and consumed the pellets following a correct arm entry. These data could indicate that the treated rats were unable to inhibit responding to already entered arms. The treated animals "remembered" the reference memory aspects of the task (i.e., leave central arena, enter arm, consume pellet in food trough, exit arm, etc.) however, they could not differentiate between previously entered and non-entered arms during a test session. That is, they appeared unable to perform the short-term working memory components of the task (i.e., remembering which arms were chosen during a session). This hypothesis is consistent with one advanced by Olton and colleagues [26,27] to explain the behavioral deficits seen in maze performance following hippocampal lesions.

Analysis of response patterns in TMT-treated rats suggests that these animals utilized a different behavioral strategy than controls to solve the maze. For example, it is commonly reported [9,29] that the response preference of control animals is to select an arm immediately adjacent to one they have just exited (see Fig. 6). In the present study the controls entered the adjacent arm on approximately 40% of their selections. While this is a preferred strategy over time it is not essential for effective maze performance since the untreated rats varied their daily choice preferences without altering their accuracy in the maze. Therefore, the response pattern of control animals exhibits a certain degree of plasticity. Animals with damage to the fimbia-fornix [29], the septal nucleus [2], or to specific hippocampal regions, as reported here, exhibit a different spatial pattern of responses such that they shift their selections to more distant arms (i.e., 2–4 arms away). Such a different pattern could indicate that rats with hippocampal damage adopt a less adaptive strategy for solving the maze. Furthermore, it might indicate that their behavior comes under the control of different, and perhaps, less relevant situational cues (i.e., intra- vs extra-maze or intero- vs exteroceptive stimuli, etc.) than the untreated rats [37]. If, for example, the rats treated with TMT developed a response algorithm of "choose every second arm" they would ultimately repeat sequences of arm entries and perseverate their responding to no-longer baited feeders. Since animals in the present experiment were not confined following arm selections, a procedure which disrupts the spatial patterning of responding without altering accuracy of maze performance (see [29]) the underlying cognitive deficits responsible for the impaired maze performance cannot be defined with certainty. Regardless of the interpretation however, the results presented here clearly demonstrate that acute TMT administration produces a long-term, and perhaps permanent, impairment in the performance of a radial-arm maze task.

An unexpected finding during the second reacquisition period was a pronounced and persistent hyperactivity in the TMT-treated group. This delayed onset of hyperactivity is unlike the reported time-course of activity changes following hippocampal lesions [19] or TMT administration [32]. These activity changes could reflect the consequences of some unspecified neural reorganization (see [1]) following hippocampal insult or the animals adopting a new behavioral strategy

to contend with the demands of the task. It was observed during the second reacquisition period that temporal efficiency was not different between groups. Although the treated animals were less accurate and required more selections they were able to obtain all the pellets within a session in about the same amount of time as the controls. The increased activity of the TMT-treated animals might therefore, be a behavioral strategy which compensated for their impaired cognitive abilities.

In the present study we observed a specific distribution of hippocampal damage, localized primarily in CA3, in all rats treated with TMT. While the length of the pyramidal cell line was significantly correlated with maze performance it accounted for only a portion of the variability in the behavioral measures. These findings could indicate that (1) length of the pyramidal cell line did not accurately reflect the extent of the hippocampal damage produced by TMT in these rats or (2) damage to structures other than the hippocampus contributes to the performance deficits observed here. Amygdala damage, which has been observed following TMT [5], is not reported to disrupt radial-arm maze performance [3]. However, Mishkin and colleagues [23,24] have observed a marked potentiation of memory impairments in monkeys exposed to combined hippocampal-amygdala insult. In light of these observations it might be useful for future studies to address whether combined damage to these limbic regions contributes to the behavioral deficits observed here.

The results of the present study are consistent with an extensive literature demonstrating that hippocampal damage produces long-term impairments in a variety of maze situations. Experimental destruction of the hippocampus disrupts the acquisition and performance of rats in a Hebb-Williams maze [12,25], Lashley III [14] and other complex spatial mazes [18] in addition to the radial-arm maze. Furthermore, humans with bilateral temporal lobe damage, involving the hippocampus are deficient in performing a visual maze task [22]. The results of these studies support the hypothesis that the hippocampus plays an important role in learning and memory processes. Moreover, there is now evidence that the hippocampal cell fields are differentially involved in the mediation of certain behaviors (see [15,20]). For example, Jarrard [16,17] reported that selective damage to either the fimbia or dorsal fornix, which would disconnect the dorsal hippocampus (CA3-CA4) from subcortical regions, selectively impaired post-operative performance in the radial-arm maze. Similar deficits were not observed following lesions to the CA1 cell field or the alveus. A report by Handelman and Olton [13] demonstrated that selective destruction of CA3 pyramidal neurons with intrahippocampally applied kainic acid produced impairments in radial-arm maze performance. Taken together, these studies indicate that pyramidal cells in CA3 or their connections play an important role in the acquisition and retention of radial-arm maze performance. A problem associated with attempts to isolate the neural substrates of behavior by using conventional lesion techniques, however, is that damage cannot be restricted to circumscribed regions and therefore incidental damage to fibers of passage and surrounding areas must be considered in any analysis of lesion-induced behavioral changes. Since systemically administered TMT exerts a regionally specific effect on the hippocampus it might be a useful tool for elaborating the differential involvement of hippocampal cell fields and their associated fiber systems in learning and memory. It has already been reported, for example, that TMT administration disrupts performance in both the radial-arm maze, as reported here, and a Hebb-Williams maze [33], and impairs the acquisition and retention of both passive [36] and active [21] avoidance responses. Thus, futher studies on the biochemical and neural correlates of TMT-induced behavioral changes are likely to provide important insights into the neurobiology of learning and memory.

ACKNOWLEDGEMENT

The authors would like to thank Drs. David Olton, David Eckerman, Michael Gage and Robert MacPhail for their constructive comments on this manuscript.

REFERENCES

1. Bar, P. R., W. H. Gispen and R. L. Isaacson. Behavioral and regional neurochemical sequelae of hippocampal destruction in the rat. *Pharmac. Biochem. Behav.* **14**: 305–312, 1981.
2. Beatty, W. W. and C. P. Carbone. Septal lesions, intramaze cues and spatial behavior in rats. *Physiol. Behav.* **24**: 675–678, 1980.
3. Becker, J. T., J. A. Walker and D. S. Olton. Neuroanatomical bases of spatial memory. *Brain Res.* **200**: 307–320, 1980.
4. Bouldin, T. W., N. D. Goines, C. R. Bagnell and M. R. Krigman. Pathogenesis of trimethyltin neuronal toxicity: Ultrastructural and cytochemical observations. *Am. J. Path.* **104**: 237–249, 1981.
5. Brown, A. W., W. N. Aldridge, B. W. Street and R. D. Verschoyle. The behavioral and neuropathologic sequelae of intoxication by trimethyltin compounds in the rat. *Am. J. Path.* **97**: 59–82, 1979.
6. *Criterion for a Recommended Standard: Occupational Exposure to Organotins*. Washington DC: National Institute of Occupational Safety and Health, 1976.
7. Dyer, R. S., T. L. Deshields and W. F. Wonderlin. Trimethyltin-induced changes in gross morphology of the hippocampus. *Neurobehav. Toxicol. Teratol.* **4**: 141–147, 1982.
8. Dyer, R. S, T. J. Walsh, W. F. Wonderlin and M. Bercegeay. The trimethyltin syndrome in rats. *Neurobehav. Toxicol. Teratol.* **4**: 127–133, 1982.
9. Eckerman, D. A., W. A. Gordon, J. D. Edwards, R. C. MacPhail and M. I. Gage. Effects of scopolamine, pentobarbital and amphetamine on radial arm maze performance in the rat. *Pharmac. Biochem. Behav.* **12**: 595–602, 1980.
10. EPA Report No. 560/–6–76–011. *The Manufacture and Use of Selected Alkyltin Compounds*. 1976.
11. Fortemps, E., G. Amand, A. Bomboir, R. Lauwerys and E. C. Laterre. Trimethyltin poisoning: Report of two cases. *Int. Archs occup. envir. Hlth* **41**: 1–6, 1978.
12. Gross, C. G., S. L. Chorover and S. M. Cohen. Caudata, cortical, hippocampal and dorsal thalamic lesions in rats: alternation and Hebb-Williams maze performance. *Neuropsychologia* **3**: 53–68, 1965.
13. Handelman, G. E. and D. S. Olton. Spatial memory following damage to hippocampal CA3 pyramidal cells with kainic acid: impairment and recovery with preoperative training. *Brain Res.* **217**: 41–58, 1981.
14. Jackson, W. J. and P. N. Strong, Jr. Differential effects of hippocampal lesions upon sequential tasks and maze learning by rats. *J. comp. physiol. Psychol.* **68**: 442–450, 1969.
15. Jarrard, L. E. Anatomical and behavioral analysis of hippocampal cell fields. *J. comp. physiol. Psychol.* **90**: 1035–1050, 1976.

16. Jarrard, L. E. Selective hippocampal lesions: Differential effects on performance by rats of a spatial task with preoperative versus postoperative training. *J. comp. physiol. Psychol.* **92:** 1119–1127, 1978.
17. Jarrard, L. E. Selective hippocampal lesions and behavior. *Physiol. Psychol.* **8:** 198–206, 1980.
18. Kimble, D. P. and E. Dannen. Persistent spatial maze-learning deficits in hippocampal-lesioned rats across a 7-week postoperative period. *Physiol. Psychol.* **5:** 409–413, 1977.
19. Lanier, L. P. and R. L. Isaacson. Activity changes related to the location of lesions in the hippocampus. *Behav. Biol.* **13:** 59–69, 1976.
20. Livesey, P. J. Fractionation of hippocampal function in learning. In: *The Hippocampus. vol. 2, Neurophysiology and Behavior*, edited by R. L. Isaacson and K. H. Pribram. New York: Plenum Press, 1975, pp. 279–307.
21. Mactutus, C. F., J. J. Valdes, J. S. Young and Z. Annau. Trimethyltin neurotoxicity: A potential tool for learning and memory. *Soc. Neurosci. Abstr.* **7:** 647, 1981.
22. Milner, B. Visually-guided maze learning in man: Effects of bilateral hippocampal, bilateral frontal and unilateral cerebral lesions. *Neuropsychologia* **3:** 317–338, 1965.
23. Mishkin, M. Memory in monkeys severely impaired by combined but not seperate removal of amygdala and hippocampus. *Nature* **273:** 297–298, 1978.
24. Murray, E. A. and M. Mishkin. Role of the amygdala and hippocampus in tactual memory. *Soc. Neurosci. Abstr.* **7:** 237, 1981.
25. Myhrer, T. and B. Kaada. Locomotor, avoidance and maze behavior in rats with dorsal fornix transected. *Physiol. Behav.* **14:** 847–853, 1975.
26. Olton, D. S., J. T. Becker and G. E. Handelman. Hippocampus, space and memory. *Behav. Brain Sci.* **2:** 313–365, 1979.
27. Olton, D. S., J. T. Becker and G. E. Handelman. Hippocampal function: Working memory or cognitive mapping? *Physiol. Psychol.* **8:** 239–246, 1980.
28. Olton, D. S. and R. J. Samuelson. Remembrances of placed passed: spatial memory in rats. *J. exp. Psychol.: Anim. Behav. Process.* **2:** 97–116, 1976.
29. Olton, D. S. and M. A. Werz. Hippocampal function and behavior: Spatial discrimination and response inhibition. *Physiol. Behav.* **20:** 597–605, 1978.
30. Piver, W. T. Organotin compound: Industrial applications and biological investigations. *Envir. Hlth Perspect.* **4:** 61–79, 1973.
31. Ross, W. D., E. A. Emmett, J. Steiner and R. Tureen. Neurotoxic effects of occupational exposure to organotins. *Am. J. Psychiat.* **138:** 1092–1095, 1981.
32. Ruppert, P. H., T. J. Walsh, L. W. Reiter and R. S. Dyer. Trimethyltin induced hyperactivity: Time course and pattern. *Neurobehav. Toxicol. Teratol.* **4:** 135–139, 1982.
33. Swartzwelder, H. S., J. Hepler, W. Holahan, S. E. King, H. A. Leverenz, P. A. Miller and R. D. Myers. Impaired maze performance in the rat caused by trimethyltin treatment: Problem solving deficits and perseveration. *Neurobehav. Toxicol. Teratol.* **4:** 169–176, 1982.
34. Thompson, R. F., T. W. Berger, C. F. Cegavske, M. M. Patterson, R. A. Roemer, T. J. Teyler and R. A. Young. The search for the engram. *Am. Psychol.* **31:** 209–227, 1976.
35. Thompson, R. F., T. W. Berger, S. D. Berry, F. K. Hoehler, R. E. Kettner and D. J. Weisz. Hippocampal substrate of classical conditioning. *Physiol. Psychol.* **8:** 262–279, 1980.
36. Walsh, T. J., M. Gallagher, E. Bostock and R. S. Dyer. Trimethyltin impairs retention of a passive avoidance task. *Neurobehav. Toxicol. Teratol.* **4:** 163–167, 1982.
37. Winocur, G. The hippocampus and cue utilization. *Physiol. Psychol.* **8:** 280–288, 1980.